REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 4-6 and 35-38 are newly canceled. Claims 1, 7 and 25 are amended. After amending the claims as set forth above, claims 1, 7, 8, 12-16, 25, and 28-34 are pending in this application.

Claim Objections

The Office Action objects to Claim 1 for reciting "anoligonucleotide". Claim 1 is amended to insert a space between "an" and "oligonucleotide." The amendment is clerical in nature and does not add any new matter.

The Office Action objects to Claim 25 for reciting "a oligonucleotide." Claim 25 is amended to recite "an oligonucleotide." This amendment also is clerical in nature and does not add any new matter. Claim 25 further is amended to delete the phrase "wherein the second distance is shorter than the first distance," which was added by preliminary amendment. As this amendment merely reverts to the language present in claim 25 as originally filed, no new matter is added.

Information Disclosure Statement

The Office Action indicates that "only the Abstracts of documents CN1422960 (China) and CN1422961 (China) are being considered because English language translations of the remainder of the documents have not been provided. Applicant notes that the PTO Form 1449 accompanying the 2nd Information Disclosure Statement submitted 16 November 2004 clearly states that the references were submitted as "Abstract only." However, the Examiner did not initial the PTO Form 1449, in direct contradiction to the statement in the Office Action that both of these abstracts have been considered. Applicant respectfully requests the Examiner to acknowledge his consideration of the Abstracts of CN1422960 and CN1422961 on the Form 1449.

35 U.S.C. § 102

Claims 1, 4-8, 12-16, and 35-38 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Blackburn et al. (U.S. Patent No. 6,264,825). Claim 1 is amended to recite that probe, which is immobilized to the electrode, comprises a redox moiety. Blackburn, et al. does not disclose a detector having an electrode-immobilized probe that is redox-labeled in such a manner that the redox label is closer to the electrode when the probe is bound to target as compared to when the probe is free of target. This amendment incorporates the limitations of dependent claim 5. Accordingly, no new matter is added by this amendment. Claims 4-6 and 35-38 are canceled. Claim 7 is amended to depend from claim 1, rather than now canceled claim 5.

In rejecting claim 5, the Office Action (at page 4) states, in part, that Blackburn et al teach an alternate embodiment of the detector comprising:

> an oligonucleotide probe immobilized on the electrode (e.g. Figure 5C, wherein the probe comprises elements 145, 141, 145 and 135*, and wherein the probe is immobilized to the electrode when hybridized to the target, which is immobilized to the electrode through elements 110, 111, 112, 100 and 106 of Figure 6C; column 4, lines 60-65);

Applicant submits that the Examiner is stretching the meaning of "immobilized" beyond that of common sense and certainly beyond the scope that would be understood by one of ordinary skill in the art. The standard and commonly understood meaning of "immobilized" is not movable or incapable of being moved.

The examiner relies heavily on the disclosure of Figure 5C of Blackburn et al., which is reproduced below:

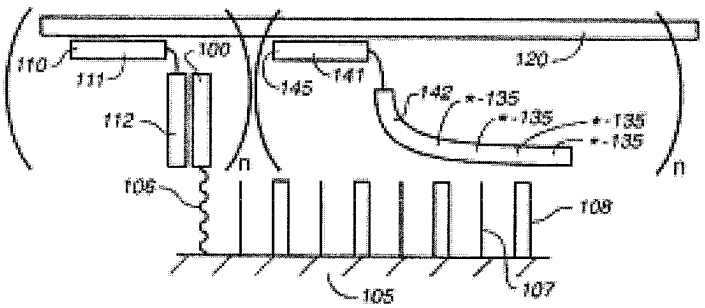

FIG._5C

The reference itself describes Figures 5C as follows:

> FIG. 5C depicts the use of two different capture probes **100** and **100'**, that hybridize to different portions of the target sequence **120**. As will be appreciated by those in the art, the 5'-3' orientation of the two capture probes in this embodiment is different.
>
> FIG. 5C depicts the use of label probes **145** that hybridize directly to the target sequence **120**. FIG. 5C shows the use of a label probe **145**, comprising a first potion [*sic*, portion] **141** that hybridizes to a portion of the target sequence **120**, a second portion **142** comprising ETMs **135**.

Clearly, the label probe **145**, which comprises the redox moiety (ETMs) is not *immobilized* to the electrode. In the absence of the target, or even of the extender (**110, 111** and **112**), the label probe **145** is free in solution, and in no way could be described as being immobilized to the electrode. To the contrary, claim 1, as amended, requires that the probe comprising the redox moiety be immobilized to the electrode, as exemplified in Figures 2 and 3, and at paragraph **[0046]** of the present application. Since Blackburn et al. fails to disclose every limitation of current claim 1, Applicant submits that this reference does not anticipate claim 1, or any of its dependent claims 7, 8 and 12-16. Applicant respectfully requests withdrawal of the rejection.

35 U.S.C. § 103

Claims 25 and 28-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Blackburn et al. (U.S. Patent No. 6,264,825) in view of Lizardi et al. (U.S. Patent No. 5,312,728). Applicant traverses the rejection, as the Examiner has failed to present a *prima facie* case of obviousness.

To establish a *prima facie* case of obvious, three basic criteria must be met:

1. there must be some suggestion or motivation in the references themselves, to modify the reference or combine the reference teachings;

2. there must be a reasonable expectation of success; and

3. the prior art references, when combined, must teach or suggest every element of the claim.

At a minimum, the Examiner has failed to demonstrate (1) a suggestion or motivation to combine the teachings of Blackburn et al with those of Lizardi et al and (2) that the references when combined teach or suggest every limitation of claim 25.

First, the Examiner has determined that "Blackburn et al do not teach the probe is a single molecule wherein first and second loops in the second region that are disrupted by hybridization to the target." Applicant agrees that nowhere does Blackburn et al disclose self-complementary hybridization within the probe. The Examiner posits that Lizardi et al cures the deficiency of Blackburn et al. Applicant strongly disagrees.

Claim 25 recites, in part:

> the second region being present in the probe intermediate the first and third regions and comprising a first nucleotide sequence which is complementary to and spaced apart from a second nucleotide sequence with which it self hybridizes to form a first loop which positions the redox moiety a first distance from the electrode, said first nucleotide sequence also hybridizing with the target nucleotide sequence in the target, such hybridizing with the target disrupting the first loop and permitting complementary nucleotide sequences in the second region to self hybridize to form a second loop which positions the redox moiety a second distance from the electrode, said first and second distances giving rise to distinguishable redox events detectable by the electrode

This portion of Claim 25 requires (1) that the second region of the oligonucleotide falls between the attachment point to the electrode (first region) and the redox moiety (third region) and (2) that the second region has a first nucleotide sequence (*A*) and a second nucleotide sequence (*B*). In the absence of target the first and second nucleotide sequences hybridize to form *A:B*. When target (*T*) is added, the target disrupts *A:B* and binds to the first nucleotide sequence to form *A:T*. As a result of the release of the loop formed by *A:B*, a second and

different loop may form. Thus rather than hybridization of the target disrupting the first and second loop, the language of claim 25 requires that the target hybridize specifically with the first nucleotide sequence (*A*). The first loop is disrupted because one half of the duplex that forms the loop (i.e. the *A* of *A:B*) is sequestered by hybridizing to the target.

Lizardi et al., however, teaches disruption of the first loop by a completely different mechanism. As stated at column 5, lines 25-31 of the Lizardi et al., this reference depends on the physically rigidity of duplex DNA (or RNA) to make it impossible to close a loop and thereby peels apart the stem of a stem:loop structure:

> The present invention is predicated on a simple molecular allosteric switch that works on the principle that when a nucleic acid double helix is formed between a relatively short probe sequence and a target sequence, the ends of the double helix are necessarily located at a distance from each other due to the rigidity of the double helix.

This theory is clearly illustrated in Figures 12 and 13 of Lizardi, upon which the Examiner relies in making the rejection. The Examiner states that the portion of claim 25 that recites "having a first nucleotide sequence complementary to and spaced apart from a second nucleotide sequence with which it self hybridizes to form a first loop" is supplied by elements **31-33** of Figure 12, including sequences **32** and **33**. Figure 12 illustrates a stem:loop structure in which **32** and **33** form a duplex (**32:33**) and **31** forms the interior of the loop. The Examiner goes on to indicate that the element of claim 25 requiring "the first nucleotide sequence also hybridizing with the target nucleotide sequence in the target, such hybridizing with the target disrupting the first loop" is provided by Figure 13, which illustrates the interior of the first loop **31** binding to the target. The Examiner's conclusion that Figures 12 and 13 of Lizardi illustrate the elements of claim 25 is mistaken. The elements of Figure 12 that reasonably correlate to the first nucleotide sequence and second nucleotide sequence of claim 25 would be elements **32** and **33**, which form the duplex portion of the stem:loop structure. Lizardi does not disclose the target binding to the first sequence (which must be a part of the duplex), rather Lizardi teaches binding to the intervening sequence **31** to create a rigid duplex and peeling apart elements **32** and **33**. Because Lizardi does not disclose a first nucleotide sequence that **both** hybridizes with a second nucleotide sequence to form a first loop **and** hybridizes with the target nucleotide sequence,

Lizardi in combination with Blackburn (which the Examiner grants does not disclose formation of stem:loop structures) does not disclose every element of the claimed invention.

Applicant also notes that the Office Action argues that Lizardi discloses formation of a second loop that is detectable with the added advantage that the assay is quantitative and allows exponential amplification. First, detectability of the second loop is irrelevant, because claim 25 is drawn to detectors in which a redox label is in a first and second state relative to a detector. Second, Applicant submits that because Lizardi is drawn to amplification systems, there is no motivation to combine the teachings of Lizardi with those of Blackburn. The Examiner states that:

> It therefore would have been obvious to a person or [*sic*, of] ordinary skill in the art at the time the invention was claimed to have modified the detector comprising probes as taught by Blackburn et al with the loop forming probe as taught by Lizardi et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because such a modification would have resulted in a quantitative assay that allows exponential amplification as explicitly taught by Lizardi et al.

If exponential amplification were the goal, one of ordinary skill in the art would simply follow the teachings of Lizardi without modification to include anything from Blackburn. Similarly, Blackburn is drawn to sensing the presence of targets by detecting an electron transfer. Nothing in Blackburn suggests that exponential amplification of the target is possible, never mind desirable. Accordingly, the motivation cited by the examiner finds no support in the disclosure of either Blackburn et al or Lizardi et al.

Therefore, the Examiner has failed to present a *prima facie* case of obvious because (1) the references when combine do not disclose every element of the invention of claims 25 and 28-34 and (2) one of ordinary skill in the art would not be motivated to combine the references. Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103(a).

Double Patenting

Claims 1, 4-8, 12-16, 25 and 28-35 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of

copending Application No. 11/193,318. The rejection is provisional because the allegedly conflicting claims have not been patented. Applicant requests that the rejection be held in abeyance until an actual obviousness-type double patenting rejection can be presented.

Similarly, claims 1, 4, 5, 7, 8, 12-16, 25 and 28-38 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-6, 8-11, 13-17, and 20-52 of copending Application No. 10/678,760. The rejection is provisional because the allegedly conflicting claims have not been patented. Applicant requests that the rejection be held in abeyance until an actual obviousness-type double patenting rejection can be presented.

Claim Interpretation

The Office Action invites Applicant to explain a different embodiment of claim 36 which illustrates the embodiment wherein the target comprising the redox moiety is **closer** to the electrode in the **absence** of hybridization. Claim 36 is canceled, thereby mooting the Examiner's invitation.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 21 November 2006 By _____

FOLEY & LARDNER LLP
Customer Number: 38706
Telephone: (650) 251-1115
Facsimile: (650) 856-3710

Karen E. Flick
Attorney for Applicant
Registration No. 44,111